

Asymptomatic COVID-19 and structural changes in the brain

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ABSTRACT

Aims: Neurological symptoms are the most prevalent extrapulmonary complications of coronavirus disease 2019 (COVID-19). In this context, the objective of this study is to assess the brain magnetic resonance imaging (MRI) parameters of asymptomatic COVID-19 individuals one year after diagnosed with COVID-19 in comparison with healthy control subjects.**Methods:** The population of this prospective study consisted of individuals who have not developed olfactory impairment or other complications within one year after diagnosed with COVID-19. For the study, 8 male, 25 female, 4 male and 23 female individuals were accepted for PCG and CG, respectively, according to the inclusion and exclusion criteria. The mean age was found to be 37.75 ± 11.56 and 37.11 ± 10.67 , respectively. All participants included in the study underwent olfactory sulcus (OS) depth, olfactory bulb (OB) volume, hippocampal sclerosis (HS), insular gyrus area, and corpus amygdala area measurements.**Results:** The bilateral OB volume, insular gyrus area and corpus amygdala area were significantly lower in the post-COVID-19 group (PCG) than in the control group (CG) ($p < 0.05$). On the other hand, the bilateral OS depth was significantly higher in PCG than in CG ($p < 0.05$). In the PCG, the insular gyrus area and corpus amygdala area values of the right side were significantly higher than those of the left side ($p < 0.05$). In addition, bilateral HS was detected in five patients in the PCG, right-sided HS in two patients, and left-sided HS in one patient.**Conclusion:** The findings of this study have shown that COVID-19 infection, albeit asymptomatic, can trigger neurodegeneration. We believe that in the future COVID-19 infection will play a role in the etiopathogenesis of many neurodegenerative diseases.**Keywords:** Olfactory bulb, insular cortex, hippocampal sclerosis, COVID-19, amygdala, prefrontal cortex

INTRODUCTION

The coronavirus disease 2019 (COVID-19) that broke out in the Wuhan City of China in December, 2019, was declared a pandemic by the World Health Organization (WHO) on March 11th, 2020, and caused numerous morbidity and mortality worldwide since then. Although the pandemic has slowed down since 2022, extensive studies are needed to determine the long-term complications that may be caused by COVID-19.^{1,2} Previous studies have demonstrated potential late complications of COVID-19 including lung fibrosis, venous and arterial thromboembolism, cardiac thrombosis, stroke, brain fog, dermatological complications, and mood dysfunctions.³⁻⁵ Although the exact mechanisms responsible for long-term complications of COVID-19 remain unknown, it has been speculated that several pathophysiological mechanisms of the coronavirus that causes COVID-19, namely severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) might account for COVID-19's longer-term complications and sequelae.¹ Neurological

symptoms are the most prevalent extrapulmonary complications of COVID-19.⁶

In view of the foregoing, this study was carried out to assess the brain MRI parameters of asymptomatic COVID-19 individuals one year after diagnosed with COVID-19 in comparison with healthy control subjects.

METHODS

Study Design

The protocol of this study was approved by the Hitit University Faculty of Medicine Ethics Committee (Date: 31.03.2022 Decision No: 2022-17). This study was carried out in accordance with the ethical principles set forth in the Declaration of Helsinki and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies. Informed consent was obtained from all participants included in this study.

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Population and Sample

The population of this prospective study consisted of individuals who have not developed olfactory impairment or other complications within one year after diagnosed with COVID-19. All participants included in the study underwent OS depth, OB volume, HS, insular gyrus area, and corpus amygdala area measurements.

None of the participants included in the study had olfactory disturbances during viral infection. The individuals who had asymptomatic COVID-19 had been diagnosed with COVID-19 using the reverse transcription-polymerase chain reaction (RT-PCR) test via nasopharyngeal swab specimens. They were infected by contact and did not have acute and/or chronic complaints during the follow-up period.

The study inclusion criteria were as follows; having been diagnosed with asymptomatic COVID-19 without complications and having had COVID-19 at least one year ago. On the other hand, the study exclusion criteria were as follows; having a trauma history, sinonasal cerebrospinal fluid leak or sinonasal surgery, sinonasal polyposis, facial and/or nasal septal deformity, Parkinson's and/or Alzheimer's disease, multiple sclerosis, epilepsy or another neurodegenerative disease.

Data Collection Procedure

The individuals in both the PCG and the CG underwent a detailed neurological examination, and were administered the Hamilton Rating Scale for Depression (HRSD) and Hamilton Anxiety Rating Scale (HARS), as well as the Montreal Cognitive Assessment (MoCA) and Mini-Mental Status Examination (MMSE). All participants were evaluated by electroencephalography (EEG). The Brief Smell Identification Test was administered to all participants.

Brain MRI Protocols

Participants' MRI images were obtained using a 1.5-Tesla MRI device at a single center. The sequences performed were axial T1-weighted spin-echo (T1W SE) MRI with and without contrast enhancement, diffusion-weighted imaging, axial and coronal T2-weighted fast-spin-echo (T2W FSE) MRI, and 2D fluid attenuated inversion recovery (FLAIR).

The measurement data from coronal T2W FSE images for OB volume and OS depth and axial FLAIR images for the insular gyrus area and axial T1W SE images for the corpus amygdala area were evaluated by a single radiologist with 12-year experience who was blinded to the study groups.

OB volume was manually measured first with an electronic cursor from the slice, where the OB image was most clearly seen on coronal T2W images, in square

millimeters, and secondly, this resulting value was multiplied by the slice thickness to obtain the volume in cubic millimeters. In order to measure the OS depth, a virtual tangent line was drawn in the posterior plane of the orbit connecting the inferior orbital gyrus and the lower edges of the gyrus recti on coronal T2W images. The OS depth was calculated by measuring a new line drawn from this tangent line to the deepest point of the OS. The area of the insular gyrus in square millimeters was measured at the level where the head of the caudate nucleus and putamen were observed and in the section where it was maximum. corpus amygdala area was measured in square millimeters in the sections where it was observed to be the largest.

Statistical Analysis

Statistical analyses were performed using the SPSS 22.0 (Statistical Product and Service Solutions for Windows, Version 22.0, IBM Corp., Armonk, NY, U.S., 2013) software package licensed by Hitit University. Independent samples t-test, paired samples t-test, chi-square test, Pearson's correlation test, and Spearman's correlation rho efficient were used in the statistical analyses. The probability (p) statistics of <0.05 were deemed to indicate statistical significance.

RESULTS

For the study, (24%) 8 male, (76%) 25 female, (15%) 4 male and (85%) 23 female individuals were accepted for PCG and CG, respectively, according to the inclusion and exclusion criteria. The mean age of the PCG was 37.75 ± 11.56 years, and the mean age of the CG was 37.11 ± 10.67 years. There was no significant difference between the groups in terms age ($p=0,748$). The bilateral OB volume was significantly lower in the PCG than in the CG ($p=0,033$). The bilateral OS depth was significantly higher in the PCG than in the CG ($p=0.041$). The comparison of the OB volume or OS depth values within the groups did not reveal any significant difference between the left and right sides ($p=0.637$). The bilateral insular gyrus area was significantly lower in the PCG than in the CG ($p=0,0347$). The bilateral corpus amygdala area was significantly lower in the PCG than in the CG ($p=0,026$). In the PCG, the insular gyrus area and corpus amygdala area of the right side were significantly higher than those of the left side ($p=0,023$). In the CG, there was no significant difference between the left and right sides in insular gyrus area and corpus amygdala area volumes of ($p=0,482$). The measurement results for the peripheral and central smell regions are shown in **Table**. Bilateral HS was detected in five patients in the PCG, right-sided HS in two patients (**Figure**), and left-sided HS in one patient. In the CG, bilateral HS was detected in only one patient. Epileptic activity and/or slow wave activity were

not observed on the EEG of any participant included in CG. Theta form slow wave activity was observed in bilateral centroparietal regions in three patients who were diagnosed with bilateral HS among the participants included in PCG. Neither group had a participant with a history of epileptic seizures. Cognitive functions were within normal limits in both groups. Participants who did not have depression or anxiety also had no olfactory impairment.

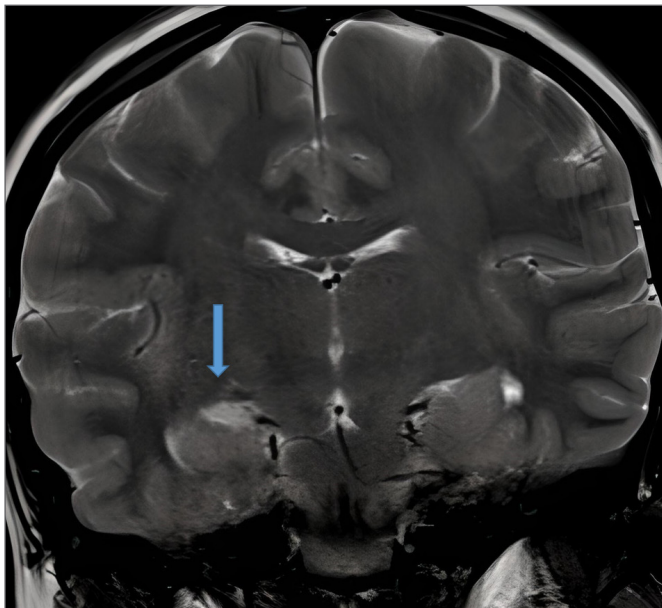


Figure. Right-sided hippocampal sclerosis

DISCUSSION

The exact mechanisms responsible for long-term complications of COVID-19 remain unknown. Nevertheless, it has been speculated that several pathophysiological mechanisms of SARS-CoV-2 virus might account for COVID-19's longer-term complications and sequelae.¹ Among these are; the entry receptor for SARS-CoV-2 angiotensin-converting enzyme 2 (ACE2), which allows the virus to enter target cells through activation of its spike protein by transmembrane serine protease 2.^{7,8} These receptors are expressed in epithelial cells, nasal goblet cells, gastrointestinal epithelial cells, pancreatic β -cells, and renal podocytes, suggesting that direct tissue damage may be the primary mechanism of COVID-19 infection as well as its longer-term complications.⁹⁻¹¹ In addition to direct cellular infection, there are several other mechanisms which may explain the pathophysiology

leading to COVID-19-related multiorgan systemic disorder, including endothelial injury, immune system dysregulation, and hypercoagulability often leading to thrombosis.¹² The autoimmune reactions reported by a study evaluating the autopsies of individuals who died due to COVID-19 provided evidence for the hypothesis of cluster of differentiation 8-positive T lymphocytes (CD8+ T cell)-mediated cytotoxicity.¹³

Various COVID-19-related neurological and psychiatric long-term complications have been reported in the literature. Long-term symptom data from different sources indicated ongoing neurological findings in COVID-19 patients two months after acute infection, including fatigue, muscle weakness, sleep difficulties, myalgia, and headache.^{14,15} In contrast, in this study, none of the participants included in PCG had such complaints.

SARS-CoV-2 reportedly may also cause neuroinvasion. As a matter of fact, postmortem brain studies reported symptoms including edema, hemorrhage, hydrocephalus, atrophy, encephalitis, infarcts, swollen axons, myelin loss, gliosis, neuronal satellitosis, hypoxic-ischemic damage, arteriolosclerosis, leptomeningeal inflammation, neuronal loss, and axon degeneration.¹⁶ As the COVID-19 pandemic progressed, a growing body of evidence indicated that SARS-CoV-2 can cause neuroinvasion and affect the central nervous system (CNS) in multiple ways.^{17,18} Neurotropism is another feature of SARS-CoV-2, and it has been reported that the endothelium, glial cells, and neurons express ACE2, which makes them a target for SARS-CoV-2.¹⁹ Also, neurological manifestations during COVID-19 infection can be caused directly by the SARS-CoV-2 in the CNS or by the host's immune response and systemic complications. After gaining access to the CNS, SARS-CoV-2 can cause immune cell infiltration and activate inflammatory pathways through the secretion of chemokines, and cytokines activate thrombotic pathways, contributing to tissue damage and causing microangiopathy.^{17,20} Brain atrophy has been reported in long COVID-19 syndrome patients. In contrast the patients included in this study survived COVID-19 asymptotically without any complications during and after the COVID-19 process. Atrophy in the orbitofrontal and parahippocampal regions has been reported in the literature in patients with cognitive impairment who have had COVID-19. In one of these studies, Crunfli et al.²¹ reported that, consistent with a model in which SARS-CoV-2 involved the CNS

Table. Measurement results in both groups

	OS depth		OB volume		Insular gyrus area		Corpus amygdala area	
	R	L	R	L	R	L	R	L
PCG	10.95 $\pm$ 1.13	10.68 $\pm$ 1.24	31.20 $\pm$ 2.83	34.75 $\pm$ 3.23	254.90 $\pm$ 53.03	241.23 $\pm$ 29.6	136.0 $\pm$ 17.33	124.90 $\pm$ 19.15
CG	8.18 $\pm$ 0.64	8.78 $\pm$ 0.79	44.01 $\pm$ 2.08	44.46 $\pm$ 3.05	303.3 $\pm$ 42.40	300.1 $\pm$ 21.8	149.9 $\pm$ 14.27	149 $\pm$ 16.9

R right, L left, PCG post covid-19 group, CG control group, OB olfactory bulb, OS Olfactory sulcus

of COVID-19 patients, SARS-CoV-2 primarily infected astrocytes via neuropilin-1 interaction, and secondarily impaired neuronal function and viability. Accordingly, it was speculated that neuroinvasion mechanisms that play a role in fatal COVID-19 may also be effective in mild COVID-19, and therefore, interventions to treat COVID-19 should also foresee ways to prevent invasion of the CNS by SARS-CoV-2 and/or replication of SARS-CoV-2 in astrocytes. Although the cases included in this study were asymptomatic, an increase was detected in HS in addition to significant changes in the olfactory bulb, cingular, and amygdala areas. In a case series featuring two patients with normal MRIs who complained of cognitive symptoms, the hypothesis that these cognitive symptoms might be associated with the dysfunction of the cingulate cortex was supported by brain and 18-F-fluorodeoxyglucose positron emission tomography (FDG PET).²² Experimental histological studies conducted on the olfactory bulb have demonstrated that synaptogenesis and neuroplasticity are likely to persist throughout life in this anatomical formation.²³⁻²⁵ In an imaging study conducted with 25 patients with cognitive impairment, a significant positive correlation was determined between the total Fear of Coronavirus Disease 2019 Scale score and a decrease in volume at the right posterior cingulate cortex.²⁶ In another retrospective study including 14 relapsing-remitting multiple sclerosis patients, the 113 longitudinal MRI images of the patients revealed the decrease in parahippocampal gyrus' volume, suggesting accelerated atrophy during or after COVID-19.²⁷ In addition, weakening in the sense of smell is reportedly an early sign of Alzheimer's disease (AD) and a predictor of the conversion from mild cognitive impairment to AD.²⁸ Al-Otaibi et al.²⁹ reported significantly smaller olfactory cortex volume in patients with AD compared to healthy older control subjects. In comparison, this study's findings supports the hypothesis that COVID-19 may be a precursor of neurodegeneration.

Recently published studies have provided evidence for the etiology of memory deficit caused by COVID-19.^{30,31} One of these studies reported a reduction in the gray matter volume such as the frontal lobe, which is responsible for working memory capacity, in certain COVID-19 patients.^{20,32} In another study, COVID-19 reportedly caused silent brain hypoxia, also contributing to hippocampal damage.^{33,34}

Previous studies speculated that a decrease in hippocampal volume in COVID-19 patients may cause cognitive deficits in memory,^{35,36} suggesting that COVID-19 patients are much more likely to experience short-term memory deficits compared to long-term memory. As a matter of fact, 50% of the MRI scans of COVID-19

patients revealed white matter hyperintensities in the frontal and parietal lobes and significant reductions in gray matter thickness bilaterally especially in the parahippocampal gyrus, anterior cingulate cortex, and temporal pole compared to healthy control subjects. In comparison, in this study, the insular gyrus area and corpus amygdala area of the left side were significantly decreased in post-COVID-19 patients compared to the right side. All participants included in this study were right-handed, that is, atrophy in both areas was in the dominant hemisphere. The literature data, including the case studies and case series, suggest that COVID-19 patients could suffer memory problems after the onset of COVID-19 even if they do not have significant past medical or neuropsychiatric condition.³⁷ The EEG studies indicated that diffuse pathological slowing, intermittent rhythmic delta-activity, and low delta band at baseline were associated with memory impairment in COVID-19 patients.³⁸⁻⁴⁰ In comparison, in this study, slow wave activity was detected on EEG in three patients with bilateral hippocampal sclerosis. Previous studies indicate that either structural abnormalities, e.g., cortical atrophy and white matter hyperintensities or functional abnormalities, e.g., hypometabolism in widespread brain regions may exist in COVID-19 patients with memory impairment compared to healthy control subjects. These brain abnormalities and memory dysfunction are likely to reverse over time in most cases. The direction, i.e. increase vs. decrease, of the anatomical and metabolic alterations initially was in line with imaging findings in patients with comparable memory impairments such as dementia and AD,^{37,41} and studies have shown that COVID-19 severity was independent of patients' memory impairments.³⁴ Structural MRI and 18F-FDG PET were the most frequently utilized imaging tools in the previous studies on the brain changes associated with memory impairment. Nonetheless, the findings of these studies are contradictory.^{42,43} Tian et al.⁴⁴ pointed out that COVID-19 patients without the manifestations of memory deficits could still have brain pathological changes such as declined global cortical thickness. Hence, decreased cortical thickness, i.e. brain atrophy, might not be necessarily a direct cause of memory impairments in COVID-19 patients. This study's findings are in line with the findings of the said two studies. Evidence from both animal and postmortem showed that elevated inflammatory chemokines, especially C-C motif chemokine ligand 11 (CCL11), found in long COVID-19 syndrome patients with cognitive symptoms, directly contributed to the increased white matter microglial reactivity particularly in the hippocampus, an area highly responsible for learning and memory. These neuroinflammatory-related changes might be directly associated with early and transient

memory impairment in COVID-19 patients.⁴⁵ Although the relationship between COVID-19 infection and neurodegenerative diseases remains unclear, a genetic relationship between Alzheimer's and COVID-19 has been found. We can think that COVID-19 will have a greater place in both etiopathogenesis and treatment in future neurodegenerative disease studies.^{46,47} Remdesivir was approved for the treatment of COVID-19 infection in 2020, but we only know that antiviral agents are not enough for treatment. Which treatments will be more effective, especially in long-term complications, still protects the dark side of the disease.⁴ Current treatments for COVID-19, using antivirals, target pathological mechanisms by reducing inflammation. Therefore, from laboratory and clinical studies in the literature, when the pathophysiological pathways underlying the neurological symptoms of long COVID-19 become more understandable, new treatment modalities will also be on the agenda.⁴⁸

Limitations

The primary limitation of this study was its relatively small sample size, which was partly due to the difficulty of finding asymptomatic COVID-19 cases who tested positive for COVID-19 during the pandemic process. In addition, another limitation is that our study does not include the parameters of neurodegeneration (cerebrospinal fluid (CSF) analysis or PET). Therefore, future studies that preferably employ 18F-FDG PET or CSF are needed to corroborate the findings of this study.

CONCLUSION

There is sufficient evidence suggesting that memory impairment is a prominent symptom of COVID-19, and likely associated with COVID-19-induced brain dysfunction. Long-term histopathological studies will help us understand the pathophysiology of COVID-19-related memory impairment. Hypometabolism, increased white matter hyperintensities, and decreased cerebral gray matter volume may be effective indicators of memory dysfunction in COVID-19 patients, but the causal relationships between these phenomena have yet to be elucidated, as have the complications caused by asymptomatic COVID-19 infection involving multiple mechanisms in the acute period. Our knowledge on the etiopathogenesis and clinical findings of long-term COVID-19 complications will increase over time. In sum, the findings of this study suggest that COVID-19 infection, even if asymptomatic, may trigger neurodegeneration, we believe that in the future COVID-19 infection will play a role in the etiopathogenesis of many neurodegenerative diseases.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was initiated with the approval of the Hitit University Faculty of Medicine Ethics Committee (Date: 31.03.2022 Decision No: 2022-17).

Informed Consent

Written consent was obtained from all participants before starting the study.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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